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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,665	01/31/2002	Christine Leib-Mosch	10737-006001	2339

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,665	LEIB-MOSCH ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10, 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-12, 20 and 21, in Paper No. 13 is acknowledged.

2. Claims 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Applicants' preliminary amendment filed 8-31-01 has been entered. Claims 3-7, 9-12, 14, 15 and 20 have been amended. Claims 1-21 are pending and claims 1-12, 20 and 21 are under consideration.

Claim Objections

3. Claim 4 is objected to because of the following informalities: The term "cytokin" in line 3 appears to be a typographical error. Changing "cytokin" to "cytokine" would be remedial. Appropriate correction is required.

4. Claims 1-9, 11, 12, 20 and 21 are objected to because of the following informalities: There should be an article "A" or "The" in front of "retroviral expression vector", "expression vector", "vector", "prokaryotic cell", "eukaryotic cell" and "retroviral vector system". Appropriate correction is required.

Specification

1. The abstract of the disclosure is objected to because the term "Summary" is used instead of the proper term "Abstract" and the "Abstract" should be a single paragraph and not exceed 150 words as indicated below. Correction is required. See MPEP § 608.01(b).

2. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a **single paragraph** on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2, 3, 5, 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "optionally" in claims 2 and 8 is vague and renders the claims indefinite. It is unclear whether the limitation following the term "optionally" is intended or not. The metes and bounds of the limitations in the claims are unclear.

The phrase "derived from" in claims 3 and 5 is vague and renders the claims indefinite. It is unclear as the metes and bounds of what would be considered "derived from". It is unclear to what extent of modification is considered "derived from".

The phrase "the group consisting of HERV-K..., ERV9, HERV-W" in claim 6 is vague and renders the claim indefinite. Changing the phrase "the group consisting of HERV-K..., ERV9, HERV-W" to "the group consisting of HERV-K..., ERV9 **and** HERV-W" would be remedial.

The term "and/or" in claim 8 is vague and renders the claim indefinite. It is unclear whether the limitation following the term "and/or" is intended to be claimed or not. Changing "and/or" to "...or...or both" would be remedial.

5. Claim 4 recites the limitation "said nucleotide sequences encoding one or more proteins or elements of therapeutic and cytokin peptides" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 7 recites the limitation "said promoter region besides the TATA box" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-12, 20 and 21 are directed to a retroviral expression vector containing DNA sequences for packaging of the vector RNA and a human endogenous retroviral DNA nucleotide sequence (HERV), such as the LTR region and the non-translated region between the 5' LTR and the gag region of the HERVs, for cell-specific expression, the mRNA or RNA of said retroviral expression vector, a host cell containing said retroviral expression vector, and a retroviral vector system comprising said retroviral expression vector and a packaging cell line comprising at least one retroviral or recombinant retroviral construct encoding packaging proteins of the retroviral expression vector.

The specification discloses the relative promoter activities of HERV-E, HERV-H, HERV-K-T47D, HERV-L and HERV-T in different cell lines *in vitro*. The claims encompass using various promoter regions of different HERVs in a retroviral vector for cell-specific expression of desired genes. The specification states "The present invention relates to retroviral expression vectors bearing promoters which may be cell-specifically controlled. The vectors are useful for example for the cell-specific expression of genes of therapeutic value in the context of a gene therapy" (specification, page 1). The claimed retroviral expression vector must have a use and the use of said retroviral expression vector is for gene therapy *in vivo* in light of the specification. Therefore, the claims read on using the claimed retroviral expression vectors or retroviral vector system for gene therapy *in vivo* in light of the specification.

The specification fails to provide adequate guidance and evidence for using a retroviral expression vector containing a HERV promoter sequence for cell-specific expression of a desired

gene such that the expressed desired gene product would be sufficiently present at a target site to provide therapeutic effect for a particular disease or disorder *in vivo* via various administration routes. The specification also fails to provide adequate guidance for the correlation between the cell-specific expressed gene product and a particular disease or disorder.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, right column). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3) and random integration of retroviral vector DNA into the host chromosome can lead to activation of unwanted genes or inactivation of transgenes (page 240, right column).

Sjottem et al., 1996 (Journal of Virology, Vol. 70, No. 1, p. 188-198) discloses that there are about 1,000 full-length elements and a similar number of solitary LTRs in HERV-H family of endogenous retrovirus-like elements and only a subset of HERV-H LTRs display promoter activity in human cell lines. Sjottem reports that members of the Sp1 protein family may be crucial for the tissue-specific expression pattern of HERV-H elements (e.g. abstract).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell

population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use various HERV LTRs in a retroviral expression vector for cell-specific expression in various cell types in a subject and sufficient expression of a desired gene product can be obtained so as to provide therapeutic effect for a particular disease or disorder for gene therapy *in vivo* via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-6, 10-12, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verma et al., 1997 (Nature, Vol. 389, pages 239-242) in view of Masahiro et al., 1995 (3-Biochem. Genetics, Vol. 122, p. 315, IDS) and Sjottem et al., 1996 (Journal of Virology, Vol. 70, No. 1, p. 188-198, IDS-AP).

Claims 1-6, 20 and 21 are directed to a retroviral expression vector containing DNA sequences for packaging of the vector RNA and a human endogenous retroviral DNA nucleotide sequence (HERV), such as the LTR region, for cell-specific expression, the mRNA or RNA of said retroviral expression vector, a host cell containing said retroviral expression vector, and a retroviral vector system comprising said retroviral expression vector and a packaging cell line

comprising at least one retroviral or recombinant retroviral construct encoding packaging proteins of the retroviral expression vector.

Verma teaches generation of retroviral vector containing transgene under the control of a viral LTRs or enhancer-promoter elements and use of packaging cells that produce viral proteins, such as gag, pol and env proteins), to assemble viral genomes and generate retroviral vector.

Verma does not teach using HERV LTRs for cell-specific expression of a transgene.

Masahiro teaches a retroviral vector containing a human endogenous virus LTR and gag region to improve expression of a heterologous gene in human cells.

Sjottem teaches that tissue-specific Sp1-related protein BTEB binds to GC/GT box in the HERV-H LTR and stimulates transcription from the LTR promoter. Sjottem reports that members of the Sp1 protein family may be crucial for the tissue-specific expression pattern of HERV-H elements (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the viral LTR as taught by Verma with human endogenous virus LTR as taught by Masahiro because they both are viral LTR nucleotide sequences and Sjottem teaches HERV-H LTR has tissue-specific promoter activity.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to improve expression efficiency of a heterologous gene in human cells as taught by Masahiro with reasonable expectation of success.

It should be noted that the use of the retroviral expression vector as discussed in the 35 U.S.C. 112 first paragraph section does not carry weight in the 103(a) rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.